Acta Neuropathol., 91, 15-22, 1996; Lim J.-H. et al., Neurosci. Res., 28, 191-200, 1997). Consequently, since transition rate and transportation rate to brain of peripherally (intraperitoneally) administered ginsenoside Rb_1 are thought to be very low, no clinical application of ginsenoside Rb_1 was kept in mind at that stage in view of the protection of hippocampal CA1 pyramidal neurons.

It has been reported by us (Sakanaka and Tanaka) that intracerebroventricular infusion of ginsenoside Rb_1 starting immediately after occlusion of the common carotid arteries for 3 or 3.5 minutes in place of the above peripheral (intraperitoneal) administration suppresses the delayed neuronal death and learning disability (Lim J.-H. et al., Neurosci. Res., 28, 191-200, 1997). Further, it has been proved by us (Sakanaka and Tanaka) that in spontaneous hypertensive stroke-prone (SH-SP) rats with permanent occlusion of the cortical branch of the unilateral middle cerebral artery (MCA) (cerebral infarction model of rats), intracerebroventricular infusion of ginsenoside Rb_1 immediately after permanent occlusion of the MCA caused a significant reduction of the infarcted area in the cerebral cortex and ameliorated the ischemia-induced place navigation disability of the animals (Zhang B. et al., J. Stroke Cerebrovasc. Dis., 7, 1-9, 1998).

Even though ginsenoside Rb_1 is effective in the direct intracerebroventricular infusion, however, it appears

impossible to apply ginsenoside Rb_1 to human transient cerebral ischemic attack (TIA) and cerebral infarction due to the problems in the route of administration similarly to other peptide growth factors (Sakanaka M. et al., Proc. Natl. Acad. Sci. USA, 95, 4635-4640, 1998; Wen T.-C. et al., J. Exp. Med., 188, 635-649, 1998).

Concerning the mechanism of neuroprotective action by peripheral (intraperitoneal) administration of ginsenoside Rb_1, we (Sakanaka and Tanaka) have reported that a culture medium previously admixed with a low concentration (1 - 100 fg/ml) of ginsenoside Rb_1 reduces neuronal necrosis caused by a hydroxyl radical inducer (ferrous sulfate) (Lim J.-H. et al., Neurosci. Res., 28, 191-200, 1997; Zhang B. et al., J. Stroke Cerebrovasc. Dis., 7, 1-9, 1998). We have presumed from the first that ginsenoside Rb_1 decreases cell membrane lipid peroxides as a result of erasing hydroxyl radicals to protect cultured nerve cells, but on the basis of our recent studies (JP98/365560, PCT/JP99/02550: "Brain cell or nerve cell-protective agents comprising ginsenoside Rb_1"), this hypothesis has been found not always to be correct.

Several reports concerning the neuroprotective effect of ginsenoside Rb_1 have been made in culture experiments. For example, high concentrations (0.11-11 μg/ml) of ginsenoside Rb_1 reduce glutamate-mediated neurotoxicity to prevent neuronal cell death (Kim Y.-C., et al., J. Neurosci. Res., 53, 426-432,

1998), and a higher concentration, approximately 500 μM (550 μ g/ml) of ginsenoside Rb_1 has a possibility to prevent apoptosis-like nerve cell death (Tanaka T. et al., The Ginseng Review, 24, 61-65, 1998; Takino I. et al., ibid., 25, 44-50, 1998). However, according to the results of our culture experiments (Sakanaka and Tanaka), high concentrations of ginsenoside Rb_1 have shown an increased neurotoxicity (Lim J.-H. et al., Neurosci. Res., 28, 191-200, 1997; Zhang B. et al., J. Stroke Cerebrovasc. Dis., 7, 1-9, 1998).

Furthermore, such high concentrations of ginsenoside Rb_1 can not be realized in an extracellular fluid in vivo, and we speculate that administration of large amounts of ginsenoside Rb_1 into human body to maintain the high extracellular concentrations of ginsenoside Rb_1 is impossible, considering its cost and adverse effects. Actually, from our experimental results (Sakanaka and Tanaka), it has been proven that a high dose of ginsenoside Rb_1 can not always provide preferable efficacy and effectiveness (Zhang B. et al., J. Stroke Cerebrovasc. Dis., 7, 1-9, 1998).

We have aimed at elucidation of the mechanism underlying the neuroprotective action of ginsenoside Rb_1 and at the invention relating to new efficacy and applicability of the said compound, and have demonstrated up to now the suppressive effect of low concentrations of ginsenoside Rb_1 on nerve cell death (JP98/365560, PCT/JP99/02550: "Brain cell or nerve cell-